Reporting Adverse Reactions and HCT/P Deviations

FDA AND THE NEW PARADIGM FOR TISSUE REGULATION

February 1-3, 2005

Dallas, Texas

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Office of Compliance and Biologics Quality

Center for Biologics Evaluation and Research

Food and Drug Administration

Subpart E – Additional Requirements for Establishments Described in 21 CFR 1271.10

- 1271.330 Applicability
- 1271.350 Reporting

[Effective May 25, 2005]

21 CFR 1271.330 - Applicability

- Nonreproductive HCT/Ps, and
- Regulated solely under PHS Section 361
  - Reproductive HCT/Ps (semen, oocyte, embryo) –reporting not required at this time

21 CFR 1271.350 - Reporting

(a) Adverse reaction reports

(b) Reports of HCT/P deviations

– What, when, and how?

Adverse reaction reporting (21 CFR 1271.350(a))

Adverse reaction means a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response.

[21 CFR 1271.3(y)]

Adverse Reaction Reports

You must ***investigate any*** adverse reaction involving a communicable disease related to an HCT/P that you made available for distribution.

[21 CFR 1271.350(a)(1)]

Adverse Reaction Reports

You must ***report*** to FDA an adverse reaction involving a communicable disease if it

- Is fatal
- Is life-threatening
- Results in permanent impairment of function or perm damage to body structure; or
- Necessitates medical or surgical intervention, including hospitalization

MMWR Reports of Tissue Related Infections

Year	Transplanted Tissue	Organism(s)
2003	**Anterior Cruciate Ligament**	**Group A Streptococcus**
2003	**Corneal transplant**	**Clostridium**
2002	**Musculoskeletal tissues**	**Gram negative bacteria, Clostridium, polymicrobial**
2002	**Vein, tendons**	**Hepatitis C**
2001	**Knee allografts**	**Clostridium**
2000	**Anterior Cruciate Ligament**	**Various bacteria (pseudomonas, klebsiella)**

When must I report HCT/P adverse reactions?

- You must submit each report within 15 calendar days of initial receipt of the information
- You must submit followup reports within 15 calendar days of the receipt of new information

Who must report adverse reactions?

- “You” must report to FDA an adverse reaction involving a communicable disease related to an HCT/P that you made available for distribution if…
- Establishments that manufacture HCT/Ps
- Establishments that made HCT/Ps available for distribution

How do I report HCT/P adverse reactions?

- Use Form FDA 3500A (MedWatch)
- Obtained from CBER, or electronically from www.fda.gov/medwatch or www.hhs.gov/forms
- Submit 2 copies of each report to:

  Center for Biologics Evaluation and Research

  HFM-210

  1401 Rockville Pike, Suite 200N

  Rockville, MD 20852

Reporting Adverse Reactions with MedWatch Form:

Form FDA 3500A

(3500 for Voluntary)

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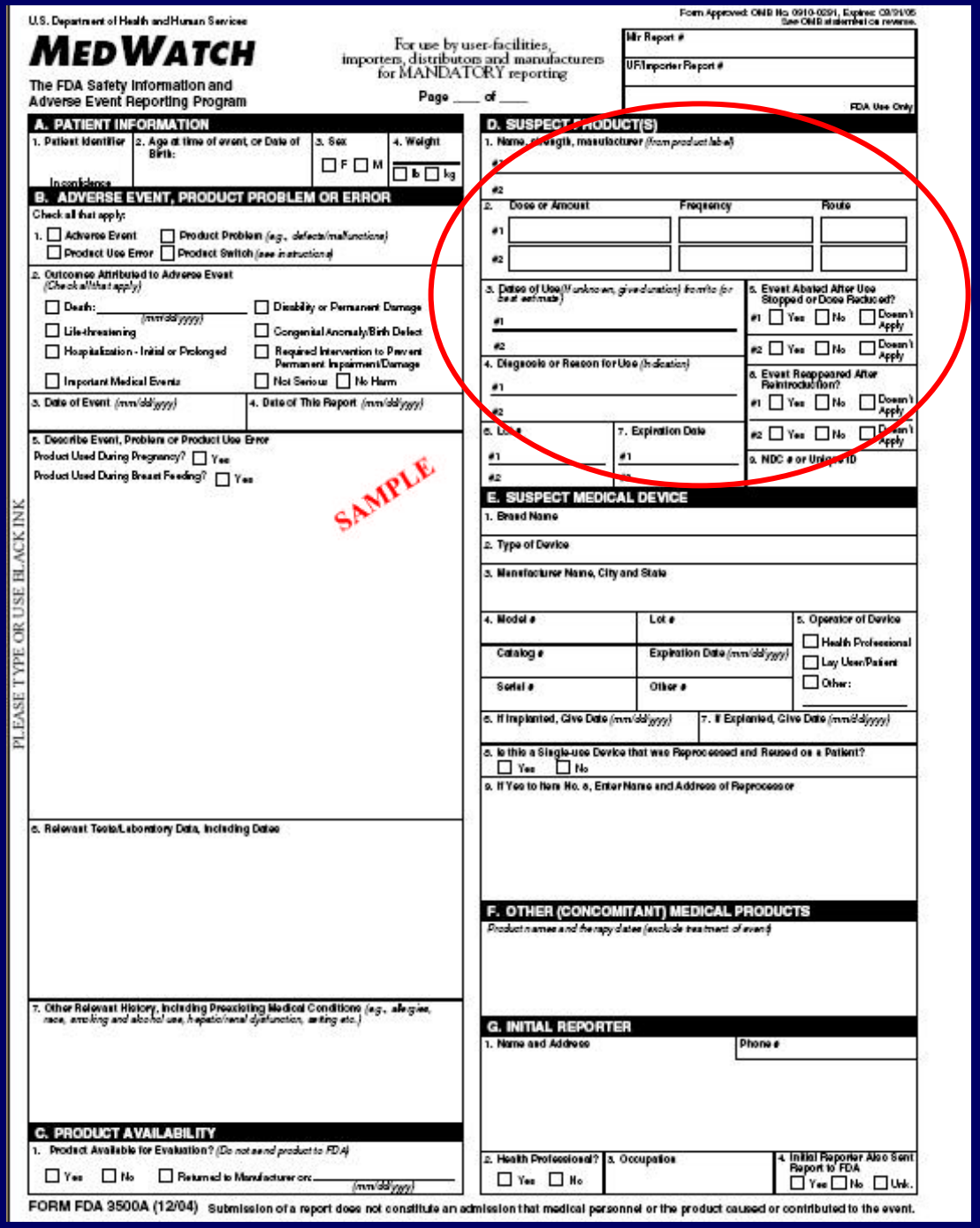


U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page ___ of ___

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

Mfr Report #

UF/Importer Report #

FDA Use Only

A. PATIENT INFORMATION

1. Patient Identifier (In confidence)
2. Age at time of event, or Date of Birth:
3. Sex ☐ F ☐ M
4. Weight ☐ lb ☐ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☐ Adverse Event ☐ Product Problem (e.g., defects/malfunctions) ☐ Product Use Error ☐ Product Switch (see instructions)
2. Outcomes Attributed to Adverse Event (Check all that apply)
   - ☐ Death: ___ (mm/dd/yyyy)
   - ☐ Life-threatening
   - ☐ Hospitalization - Initial or Prolonged
   - ☐ Important Medical Event
   - ☐ Disability or Permanent Damage
   - ☐ Congenital Anomaly/Birth Defect
   - ☐ Required Intervention to Prevent Permanent Impairment/Damage
   - ☐ Not Serious ☐ No Harm
3. Date of Event (mm/dd/yyyy)
4. Date of This Report (mm/dd/yyyy)
5. Describe Event, Problem or Product Use Error
   Product Used During Pregnancy? ☐ Yes
   Product Used During Breast Feeding? ☐ Yes

SAMPLE

PLEASE TYPE OR USE BLACK INK

6. Relevant Tests/Laboratory Data, Including Dates
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, smoking and alcohol use, hepatic/renal dysfunction, writing etc.)

C. PRODUCT AVAILABILITY

1. Product Available for Evaluation? (Do not send product to FDA)
   ☐ Yes ☐ No ☐ Returned to Manufacturer on: ___ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, strength, manufacturer (from product label)
   #1
   #2
2. Dose or Amount / Frequency / Route
   #1
   #2
3. Dates of Use (If unknown, give duration) from/to (or best estimate)
   #1
   #2
4. Diagnosis or Reason for Use (Indication)
   #1
   #2
5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply
6. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply
7. Lot #
   #1
   #2
8. Expiration Date
   #1
9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (mm/dd/yyyy) / Serial # / Other #
5. Operator of Device: ☐ Health Professional ☐ Lay User/Patient ☐ Other:
6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

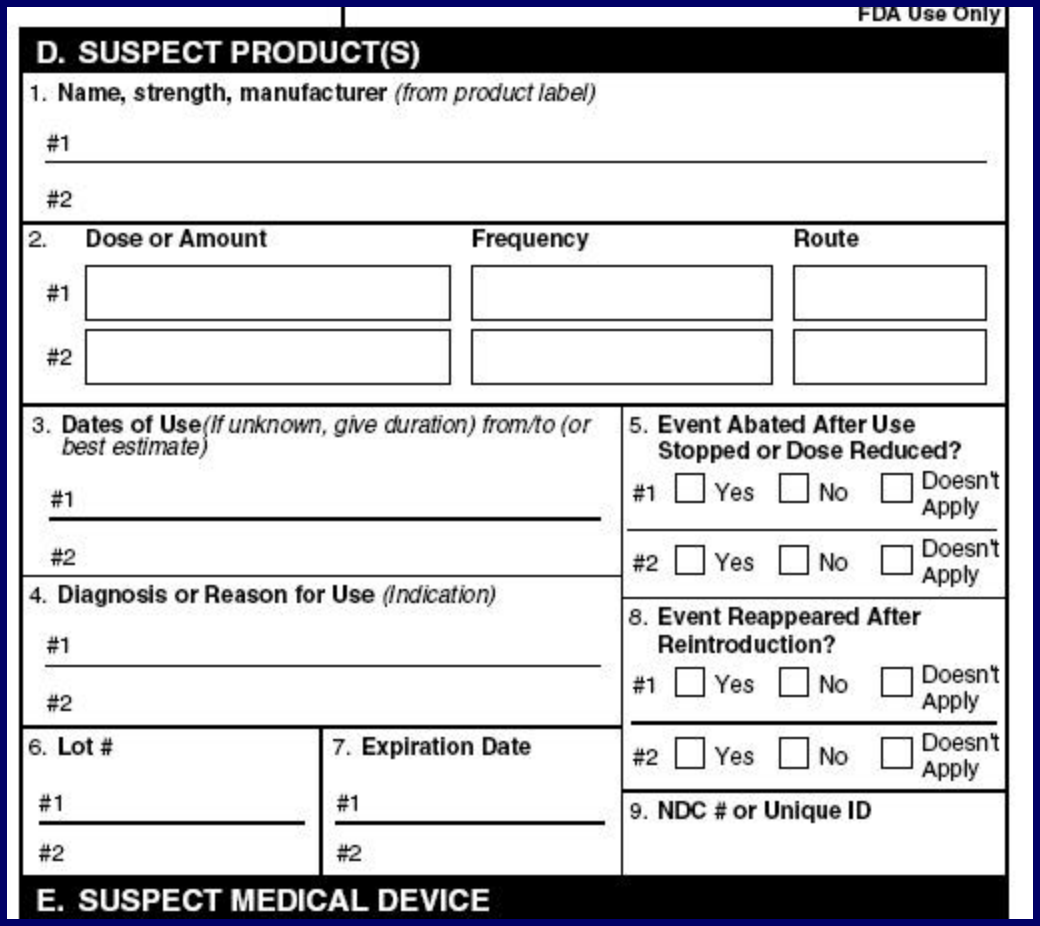
G. INITIAL REPORTER

1. Name and Address
   Phone #
2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Initial Reporter Also Sent Report to FDA ☐ Yes ☐ No ☐ Unk.

FORM FDA 3500A (12/04) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Reporting Adverse Reactions with MedWatch Form

Use **Section D for Suspect Product(s)** *not* Section E for Suspect Device



FDA Use Only

D. SUSPECT PRODUCT(S)

1. **Name, strength, manufacturer** *(from product label)*

#1

#2

2.	Dose or Amount	Frequency	Route
#1			
#2			

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*

#1

#2

4. **Diagnosis or Reason for Use** *(Indication)*

#1

#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. **Event Abated After Use Stopped or Dose Reduced?**

#1 ☐ Yes ☐ No ☐ Doesn't Apply

#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**

#1 ☐ Yes ☐ No ☐ Doesn't Apply

#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. **NDC # or Unique ID**

E. SUSPECT MEDICAL DEVICE

Reporting Adverse Reactions with MedWatch Form:

Form FDA 3500A

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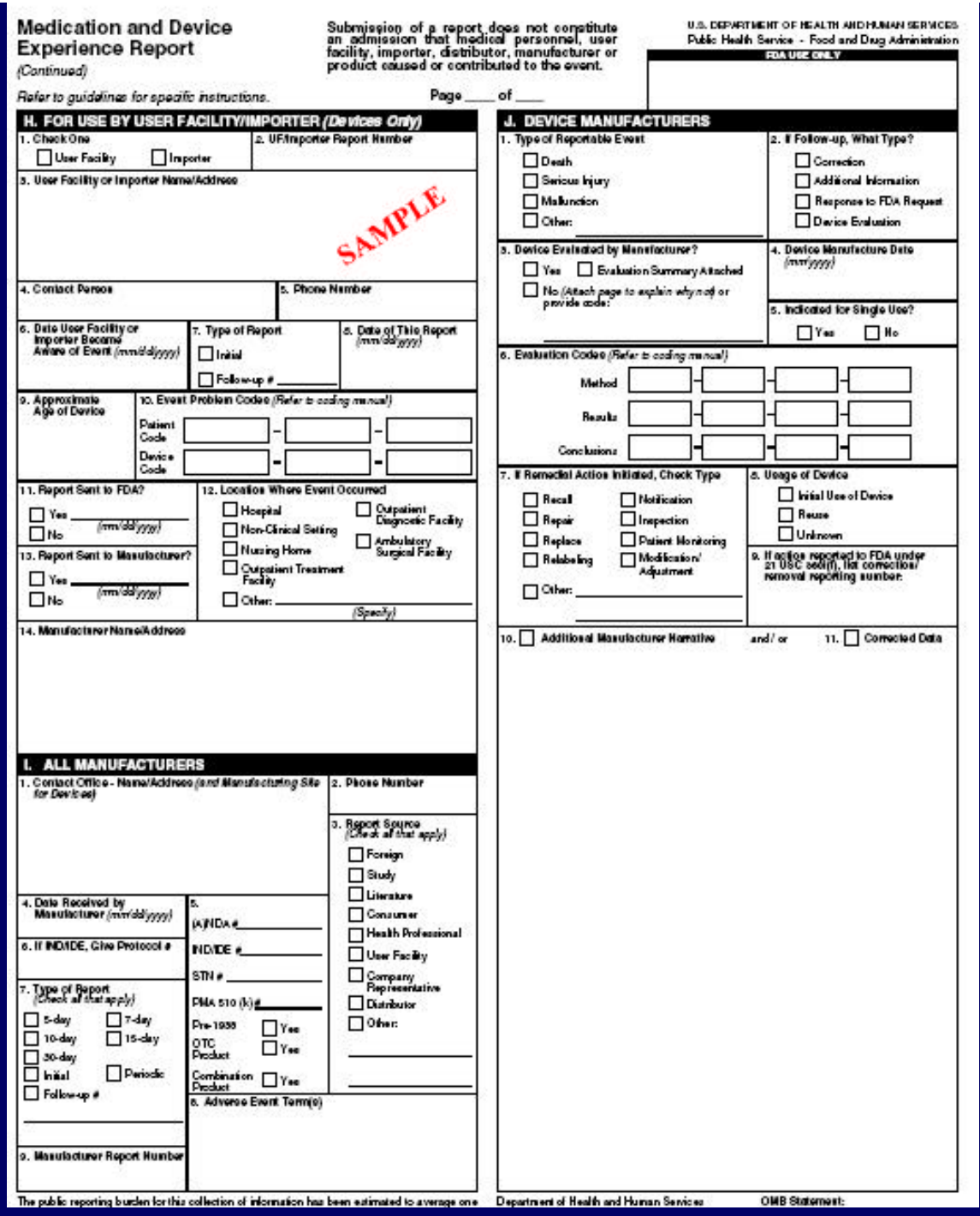

Medication and Device Experience Report
(Continued)

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service - Food and Drug Administration

FDA USE ONLY

Refer to guidelines for specific instructions.

Page ____ of ____

H. FOR USE BY USER FACILITY/IMPORTER *(Devices Only)*

1. Check One: ☐ User Facility ☐ Importer
2. UF/Importer Report Number
3. User Facility or Importer Name/Address
SAMPLE
4. Contact Person
5. Phone Number
6. Date User Facility or Importer Became Aware of Event *(mm/dd/yyyy)*
7. Type of Report: ☐ Initial ☐ Follow-up # ____
8. Date of This Report *(mm/dd/yyyy)*
9. Approximate Age of Device
10. Event Problem Codes *(Refer to coding manual)*: Patient Code ___ - ___ - ___; Device Code ___ - ___ - ___
11. Report Sent to FDA? ☐ Yes ____ *(mm/dd/yyyy)* ☐ No
12. Location Where Event Occurred: ☐ Hospital ☐ Outpatient Diagnostic Facility ☐ Non-Clinical Setting ☐ Ambulatory Surgical Facility ☐ Nursing Home ☐ Outpatient Treatment Facility ☐ Other: ____ *(Specify)*
13. Report Sent to Manufacturer? ☐ Yes ____ *(mm/dd/yyyy)* ☐ No
14. Manufacturer Name/Address

I. ALL MANUFACTURERS

1. Contact Office - Name/Address *(and Manufacturing Site for Devices)*
2. Phone Number
3. Report Source *(Check all that apply)*: ☐ Foreign ☐ Study ☐ Literature ☐ Consumer ☐ Health Professional ☐ User Facility ☐ Company Representative ☐ Distributor ☐ Other: ____
4. Date Received by Manufacturer *(mm/dd/yyyy)*
5. (A)NDA # ____ IND/IDE # ____ STN # ____ PMA 510 (k) # ____ Pre-1938 ☐ Yes OTC Product ☐ Yes Combination Product ☐ Yes
6. If IND/IDE, Give Protocol #
7. Type of Report *(Check all that apply)*: ☐ 5-day ☐ 7-day ☐ 10-day ☐ 15-day ☐ 30-day ☐ Initial ☐ Periodic ☐ Follow-up # ____
8. Adverse Event Term(s)
9. Manufacturer Report Number

J. DEVICE MANUFACTURERS

1. Type of Reportable Event: ☐ Death ☐ Serious Injury ☐ Malfunction ☐ Other: ____
2. If Follow-up, What Type? ☐ Correction ☐ Additional Information ☐ Response to FDA Request ☐ Device Evaluation
3. Device Evaluated by Manufacturer? ☐ Yes ☐ Evaluation Summary Attached ☐ No *(Attach page to explain why not or provide code:)* ____
4. Device Manufacture Date *(mm/yyyy)*
5. Indicated for Single Use? ☐ Yes ☐ No
6. Evaluation Codes *(Refer to coding manual)*: Method ___ - ___ - ___ - ___; Results ___ - ___ - ___ - ___; Conclusions ___ - ___ - ___ - ___
7. If Remedial Action Initiated, Check Type: ☐ Recall ☐ Notification ☐ Repair ☐ Inspection ☐ Replace ☐ Patient Monitoring ☐ Relabeling ☐ Modification/ Adjustment ☐ Other: ____
8. Usage of Device: ☐ Initial Use of Device ☐ Reuse ☐ Unknown
9. If action reported to FDA under 21 USC 360(i), list correction/ removal reporting number:
10. ☐ Additional Manufacturer Narrative and / or 11. ☐ Corrected Data

The public reporting burden for this collection of information has been estimated to average one

Department of Health and Human Services

OMB Statement:

MedWatch forms: http://www.fda.gov/medwatch/

FDA U.S. Food and Drug Administration Department of Health and Human Services

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MEDWATCH The FDA Safety Information and Adverse Event Reporting Program

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Get safety alerts by e-mail

Welcome to MedWatch, your Internet gateway for timely safety information on the drugs and other medical products regulated by the U.S. Food and Drug Administration.

What's New

Cordarone (amiodarone HCl) - New Medication Guide issued, to be provided with each prescription dispensed to patients.
(Posted 01/10/2005)

Avastin (bevacizumab) - WARNINGS, PRECAUTIONS, ADVERSE EVENTS, and DOSAGE AND ADMINISTRATION sections of labeling updated to describe arterial thromboembolic events when Avastin is used in combination with intravenous 5-fluorouracil–based chemotherapy.
(Posted 01/06/2005)

American Health & Herbs Ministry Eye Rinse Products - Voluntary recall

Safety Information

Medical Product Reporting

Postmarketing reporting: "361 HCT/Ps" vs. "Non-361 HCT/Ps"

- 361 HCT/Ps
- 21 CFR 1271.350
- "adverse reactions"
- Threshold
- Reporting time frame
- Reporting method

- Non-361 HCT/Ps
- 21 CFR 600.80, 803, or 314.80
- Definitions
- Threshold
- Reporting time frame
- Reporting method

HCT/P DEVIATION REPORTING

21 CFR 1271.350(b)

HCT/P Deviation Reporting

- Required for 361 HCT/Ps as of May 25, 2005
- Biological Product Deviation reporting for 351 HCT/Ps already required by 21 CFR 600.14
- Nonreproductive HCT/Ps only

HCT/P Deviation means an event:
(21 CFR 1271.3(dd))

- That represents a deviation from applicable regulations in this part or from applicable standards or established specifications that relate to the prevention of communicable disease transmission or HCT/P contamination; or
- That is an unexpected or unforeseeable event that may related to the transmission or potential transmission of a communicable disease or may lead to HCT/P contamination

HCT/P Deviation Reporting (21 CFR 1271.350(b))

All HCT/P deviations related to a distributed HCT/P

- Must be investigated by the manufacturer
- Must report any such HCT/P deviation
  - That occurred in that facility or in a facility that performed a a manufacturing step for the facility under contract, agreement, or other arrangement
  - Only those related to "Core CGTPs"

Distribution
21 CFR 1271.3(bb)

- *Distribution* means any conveyance or shipment of an HCT/P that has been determined to meet all release criteria.

Core CGTPs
21 CFR 1271.150(b)

- Requirements directly related to preventing the introduction, transmission, or spread of communicable diseases
- Other requirements support the core CGTPs

Core CGTPs (10)
21 CFR 1271.150

- Facilities
- Environmental control
- Equipment
- Supplies & reagents
- Recovery
- Processing and process controls
- Labeling controls
- Storage
- Receipt, pre-distribution shipment, and distribution
- Donor eligibility determination (donor screening and donor testing)

When must I report HCT/P deviations?
21 CFR 1271.350(b)(3)

You must report each such HCT/P deviation *that relates to a core CGTP*…within 45 days of the discovery of the event.

Who must report HCT/P deviations?

- “You”
- Establishments that manufacture HCT/Ps
- If the HCT/P deviation occurred in your facility or in a facility that performed a mfr step for you under contract, agreement, or other arrangement

How do I Report HCT/P Deviations?

Report on Form FDA 3486, electronically or by mail to:

Director, Office of Compliance & Biologics Quality, CBER (HFM-600)

1401 Rockville Pike, Suite 200N

Rockville, MD 20852-1448

- http://www.fda.gov/cber/biodev/biodev.htm
- HCT/P Codes
- HCT/P deviations

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

BIOLOGICAL PRODUCT DEVIATION REPORT

FDA USE ONLY	
Date Received:	
Date Reviewed:	
BPD ID:	
BPD No.	

* Indicates required information

A. FACILITY INFORMATION

1. Reporting Establishment Information

* Reporting Establishment Name

* Street Address Line 1

Street Address Line 2

* City | * State

Country | * Zip Code

* Point of Contact

* Telephone # ( )

E-mail

2. * Reporting Establishment Identification Number

FDA Registration #

CLIA #

3. If the BPD occurred somewhere other than the above facility, please complete this Section and Section A4, otherwise continue onto Section B1.

* Establishment Name

Street Address Line 1

Street Address Line 2

* City | * State

* Country | Zip Code

4. Establishment Identification Number:

FDA Registration #

CLIA #

B. BIOLOGICAL PRODUCT DEVIATION (BPD) INFORMATION

1. Establishment Tracking #

2. Date BPD Occurred

3. * Date BPD Discovered

4. * Date BPD Reported

5. * Description of BPD *(use Page 2 for additional space)* Go To Page 2

6. * Description of Contributing Factors or Root Cause *(use Page 3 for additional space)* Go To Page 3

7. * Follow-Up *(use Page 4 for additional space)* Go To Page 4

8. * Please Enter the 6 Character BPD Code

C. UNIT / PRODUCT INFORMATION

Please check the type of product:

Blood ☐ (Continued on Page 5)

Non-Blood ☐ (Continued on Page 6)

Biological Product Deviation Report

C2. NON-BLOOD PRODUCTS

TOTAL NUMBER OF LOTS:

Lot #	Expiration Date *(MM/DD/YYYY)*	Product Type	Product Code	Disposition	Notification (Y,N)
1.)					
2.)					
3.)					
4.)					
5.)					
6.)					
7.)					
8.)					
10.)					

U.S. Food and Drug Administration

Department of Health and Human Services

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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CBER On-Line - Login Screen

If you are a first time user, please Create a New Account. If you are an existing user, please enter your User Name and Password below. If you have forgotten your password, but remember your username and e-mail address, go to the Forgot Password screen. If you need further assistance e-mail us with your account information: Contact CBER On-Line Technical Support

REMINDER:

User Names and Passwords are CASE SENSITIVE

Leading and trailing spaces will be removed from User Name and Password.

***User Name:**

***Password:**

***Application:** CBER On-Line - Main Menu

Enter CBER On-Line

***Required**

Forgot Password / Create New Account / Help

CBER On-Line Version 1.5.1

Page Updated 04/13/2004

Contact CBER On-Line Technical Support | Help

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

CBER On-Line - Main Menu

Production Applications	Welcome to CBER On-Line
Biological Product Deviation Reporting (eBPDR)	
Blood Establishment Registration (eBER)	
HCT/P Establishment Registration (eHCTERS)	

Exit CBER On-Line Application | Edit Current Account | Change Password

CBER On-Line Version 1.5.1
Page Updated 09/22/2003

Electronic Biological Product Deviation Report (eBPDR)

Select Establishment for Reporting

Enter your establishment identification number below. Be sure to select the type of establishment identification number you are entering as either a Registration (CFN or FEI) or CLIA number. Note: The default establishment identification number type is CFN.

If you wish to retrieve a saved BPD Report enter both the establishment identification number and pre-confirmation number.

*Establishment Identification Number:

*Establishment Identification Number Type:

- (•) CFN Number
- ( ) FEI Number
- ( ) CLIA Number

P

*** Required**

Continue | View Report | CBER On-Line Main Menu

eBPDR Establishment Associations | eBPDR List of Active Users

What should I do if I have questions about HCT/P deviation reporting?

- Email account for questions about HCT/P deviations: HCTP_Deviations@cber.fda.gov
- Contact CBER's Division of Inspections and Surveillance, Sharon O'Callaghan at (301) 827- 6620